Medicine Cabinet

Hypertensive therapy: attacking the renin-angiotensin system

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Competing interests: V F has received honoraria for talks on hypertensive therapy for several pharmaceutical companies, including BMS, Novartis, Merck, Astra Merck, and Pfizer

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Franklin Delano Roosevelt: a case study

Much information is available regarding the medical care of Franklin Delano Roosevelt (FDR).[1,2] Figure 1 shows FDR's blood pressures during his presidency. In 1935, FDR's pressure was at the upper end of the normal range but rose significantly over 9 years. By March 1945, FDR became ill, and Howard Bruenn, a cardiologist, was asked to examine the president. Bruenn heard rales during physical examination. A chest x-ray film showed pulmonary edema and an enlarged cardiac silhouette. Electrocardiography (ECG) gave evidence of left ventricular (LV) hypertrophy, and urinalysis showed proteinuria. FDR was manifesting several cardiovascular consequences of untreated hypertension; LV hypertrophy, congestive heart failure (CHF), and renal insufficiency.

Bruenn initiated digitalis therapy, a low-salt diet, a reduction in FDR's substantial alcohol and cigarette use, and bed rest. Within a week, FDR no longer evidenced CHF. In August 1944, he had chest pain while giving a campaign speech on a naval ship. In the captain's quarters, he complained of severe, crushing pain for 15 minutes. ECG and white blood cell count showed that he was not having a myocardial infarction (MI) but angina, another possible hypertensive complication. In radio addresses at the time of the Yalta Conference, FDR was audibly wheezing and unable to complete sentences. His blood pressure at the time approached 250/150 mm Hg. Historians believe Stalin took advantage of a debilitated president, actions that determined the fate of eastern Europe.

In April 1945, while seated for a portrait in his Georgia vacation home, FDR fell unconscious. Bruenn estimated FDR's blood pressure to be 350/195 mm Hg. The president died within the hour of another possible hypertensive complication, intracerebral hemorrhage.

Summary points

- Angiotensin-converting enzyme inhibitors (ACEIs) are first-line therapy in patients with hypertension and concurrent congestive heart failure or proteinuria or who have had myocardial infarction; they reduce morbidity and mortality in each of these patients
- Angiotensin II-receptor blockers (ARBs) are equipotent to ACEIs, β-blockers, diuretics, and calcium channel blockers for lowering blood pressure in a general population
- ARBs have excellent adverse effect profiles comparable to placebo
- In patients who cannot tolerate ACEIs, ARBs may offer an alternative, especially in patients with congestive heart failure where morbidity and mortality data with the use of ARBs are available
- Future trials will confirm whether adding an ARB to the medical regimen of patients with congestive heart failure who are already taking an ACEI will add significant incremental value

METHODS

Studies were identified by searching MEDLINE within year parameters of 1970 and 2001 using the terms *angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker,* and *angiotensin-receptor antagonist* and bibliographies of included studies. Controlled trials, case reports, and reviews were referenced.

DEVELOPMENT OF ANTIHYPERTENSIVE THERAPY

Unfortunately for FDR, the first, relatively tolerable antihypertensive agents, β-blockers and diuretic agents, did not became available until the 1950s. Since then, 28 trials have demonstrated reduction of cardiovascular morbidity and mortality with antihypertensive therapy. In 1971, the National Heart, Lung, and Blood Institute initiated the

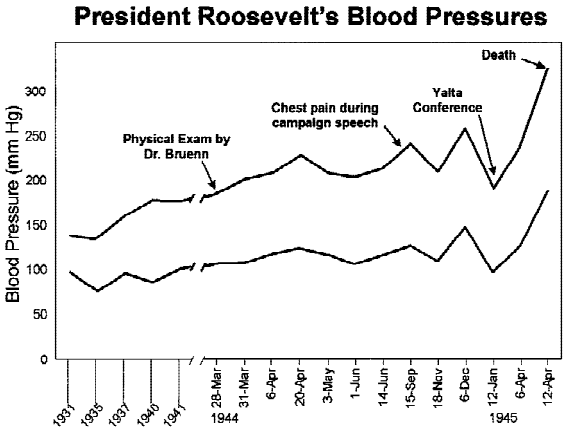
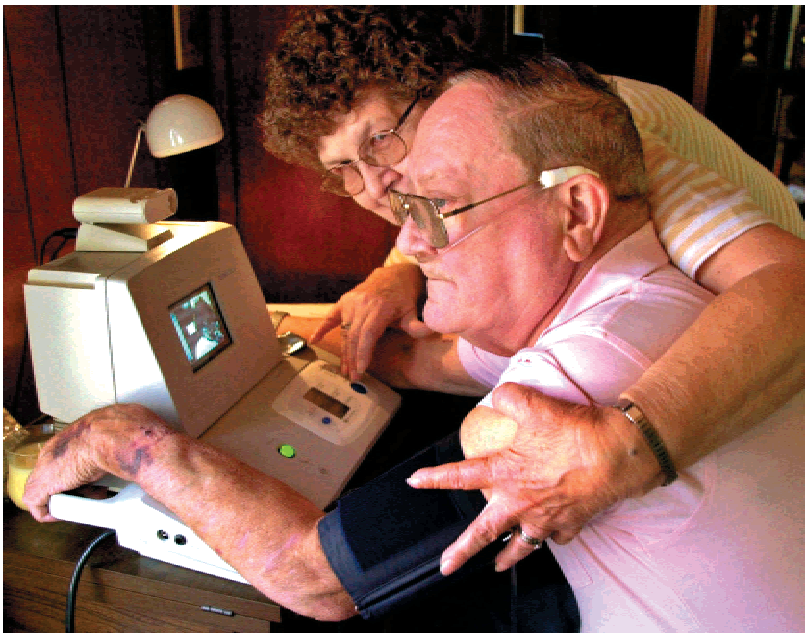


Figure 1 Systolic and diastolic blood pressures of Franklin Delano Roosevelt between 1931 and his death on April 12, 1945 (data from Ferrell[1] and Bruenn[2])

AP

Roosevelt in November 1944. Five months later, he would die of hypertensive complications

National High Blood Pressure Education Program to increase physician and patient awareness about treating hypertension. Mortality rates due to coronary heart disease and stroke have steadily decreased in the past 25 years, coincident with increased treatment of hypertension (figure 2). Since 1991 these curves have leveled off, and stroke deaths are on the rise. The National Health and Nutrition Examination Survey found a decrease in awareness and treatment of hypertension between 1991 and 1995.[3,4]



Paul Vathis/AP

This man is having his blood pressure checked by a nurse at a distance using a digital monitor

Figure 3 shows the pathophysiologic mechanisms of blood pressure regulation and hypertension.[5] Blood pressure is the product of cardiac output and peripheral vascular resistance. If either increases, blood pressure rises. β-Blocker and diuretic agents work by lowering cardiac output. Diuretics decrease intravascular fluid volume and cardiac preload; β-blockers depress cardiac inotropy and chronotropy. Although they are effective in treating hypertension and reducing mortality and morbidity, side effects limit patients' compliance with their use.

Newer drugs inhibited actions of the central or peripheral sympathetic nervous system on blood pressure; these drugs are the adrenergic inhibitors (clonidine and reserpine) and α_1-adrenergic-receptor blockers (prazosin). Although these drugs are effective, significant side effects relegated them to second-line therapy.

More recent drug development has focused on decreasing peripheral vascular resistance (figure 3). Calcium channel blockers, which inhibit calcium uptake into the vascular smooth muscle cells, are effective antihypertensive drugs with better side effect profiles than previously developed drugs.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Renin-angiotensin system

Angiotensin-converting enzyme (ACE) converts inactive angiotensin I to the active octapeptide, angiotensin II (figure 4). Angiotensin II binds to the receptors throughout the body, which affect blood pressure (figure 5). ACE, also known as kininase II, not only blocks conversion of angiotensin I to angiotensin II but also inhibits the breakdown of various kinins, including bradykinin and substance P. Until recently, it was presumed that adverse effects of angiotensin-converting enzyme inhibitors (ACEIs) were caused primarily by increased bradykinin and substance P. Data now suggest that many of the benefits of ACEIs may be partially acting through bradykinin.[6-9]

Angiotensin II

Angiotensin II binds to receptors throughout the body, acutely increasing blood pressure (figure 5). Angiotensin II also has long-term effects that are potentially detrimental to the cardiovascular system. Angiotensin II-mediated stimulation of growth factors and proto-oncogene activators within the kidney, the vasculature, and the heart result in renovascular, peripheral vascular, and myocardial hypertrophy.[10] Therefore, attacking the renin-angiotensin system should control not only hypertension but also many of its sequelae.

Brazilian pit viper

ACEIs were discovered when scientists were studying the venom of the Brazilian pit viper, *Bothrops jararacussu.* Pep-

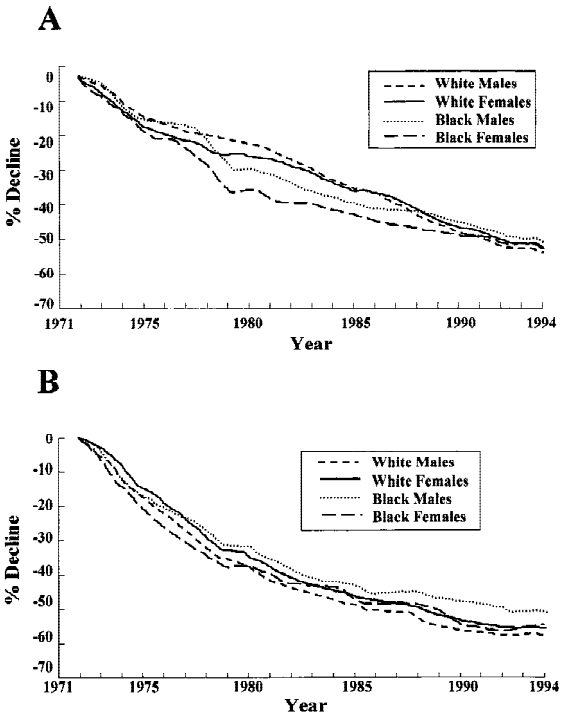


Figure 2 Percentage decline in age-adjusted mortality rates for coronary heart disease (A) and stroke by sex and race (B): United States, 1972-1994 (from the National Heart, Lung, Blood Institute; Vital Statistics of the United States, National Center for Health Statistics)

tides in the venom increased bradykinin, a substance thought to shock the viper's prey. The investigators discovered that these same peptides reduced angiotensin II levels. Four of the 5 binding ligands of the first oral ACEI developed (captopril) are similar to binding ligands of the venom peptide.[11]

ACEIs are effective in treating high blood pressure, especially in white and young patients (patients with "high-renin" hypertension). Many patients with newly diagnosed hypertension have concomitant medical issues that must be considered when choosing first-line hypertensive therapy. ACEIs play an important role as first-line therapy in many of these patients. As set forth in the treatment algorithm of the 6th Joint National Committee on the Detection, Evaluation, and Treatment of Hypertension, ACEIs are first-line therapy in diabetic patients who have proteinuria, CHF, and have had an MI.[4]

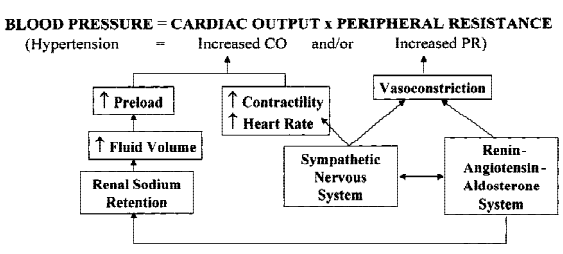


Figure 3 Determinants of blood pressure (hypertension) in the cardiovascular system based on Poiseuille's law (1842) (adapted from Kaplan[5])

Renal disease

Adding ACEIs to usual therapy in patients with type 1 diabetes mellitus who have proteinuria reduced the progression of proteinuria by 40% and lowered the combined end points of death, transplantation, or dialysis by 50%.[12] Data in patients with type 2 diabetes and those without diabetes suggest that ACEIs should be considered first-line therapy in any patient with hypertension and proteinuria. The renoprotective effects of ACEIs may be due to their unique ability to lower intraglomerular capillary pressure, in addition to the blood pressure.

CHF

Sixteen trials have demonstrated that ACEIs reduce morbidity and mortality in patients with depressed LV ejection fractions (LVEFs). The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) and SOLVD-Treatment trials showed improved survival and fewer hospital admissions in patients treated with ACEIs.[13,14] SOLVD-Prevention demonstrated decreased mortality and hospitalizations for patients with CHF who had asymptomatic LV dysfunction.[15] A meta-analysis of 16 CHF trials found a 24% survival benefit after 1 year when ACEIs were added to standard CHF therapy.[16]

After an MI

Fifteen trials demonstrated that ACEIs improved survival rates after an MI.[17,18] The benefit is seen primarily in patients with reduced LVEFs. A meta-analysis of 14 trials of ACEI use following MI found a 20% reduction after 1 year in the incidence of sudden cardiac death.[18]

There's HOPE

The Heart Outcomes Prevention Evaluation Study (HOPE) demonstrated that ACEI use significantly reduced rates of death, MI, and stroke in patients at high risk for cardiovascular disease but who do not have evidence of LV dysfunction or CHF.[19] A total of 9,500

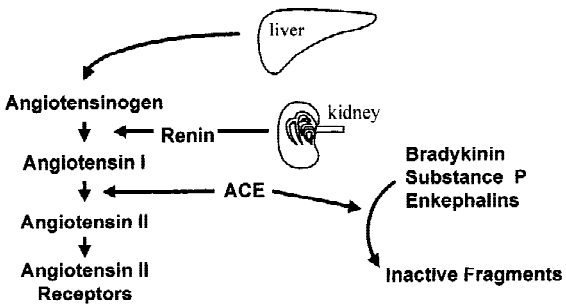


Figure 4 The renin-angiotensin system

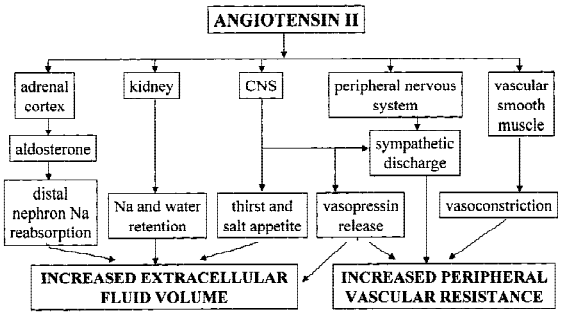


Figure 5 Angiotensin II-receptor binding affecting blood pressure (adapted from Kaplan[5])

patients (32% women) aged 55 years or older with a history of coronary artery disease, peripheral vascular disease, stroke, or diabetes mellitus and who had at least 1 other cardiac risk factor (46% had hypertension) were randomly allocated to receive an ACEI (ramipril) or placebo. After 4.5 years, there was a 22% reduction of risk for cardiovascular events with ACEI therapy. Interestingly, diabetes developed in significantly fewer patients in the group taking the ACEI. This study suggests that ACEI use has benefits beyond treating hypertension for patients at risk for cardiovascular events. To confirm these findings, a similar trial with the ACEI trandolapril is under way.

Adverse effects

A dry cough develops in 3% to 25% of patients who are taking an ACEI. This class effect is due to increased bradykinin and substance P levels and subsequent prostaglandin production, which stimulate the cough reflex in the bronchial arterial tree. Angioedema is an infrequent but potentially life-threatening adverse effect that occurs in 0.1% to 0.3% of patients receiving ACEI therapy. The incidence is higher in African Americans. Angioedema usually occurs early in ACEI therapy but has been diagnosed after more than a year. Angioedema may also be related to increased bradykinin-induced prostaglandin production, which causes histamine release.

Acute renal insufficiency and hyperkalemia can occur in elderly patients with reduced LVEFs. These patients receive diuretic therapy and become intravascularly depleted. ACE inhibition produces efferent arterial dilation that can precipitously drop the glomerular capillary pressure. The glomerular filtration rate falls, and creatinine and potassium levels rise. These adverse effects can be minimized if patients are allowed to become euvolemic before the ACEI therapy is instituted. Symptomatic hypotension is a possible adverse effect in patients with vasculopathy who have bilateral renal artery stenosis.

Is bradykinin good or bad?

It was presumed that the adverse effects of ACEIs were primarily due to increased bradykinin and that the beneficial effects were due to reduced angiotensin II. However, data suggest that the mechanisms underlying ACEI effects are more complex. Biollaz et al[20] studied the effects of enalapril in subjects with hypertension. An immediate blood pressure response occurred after 4 hours, and this effect was sustained through 6 months. Plasma ACE activity was also reduced after 4 hours and remained low over the 6-month study. At 4 hours, there was also a significant drop in angiotensin II levels, and levels appeared lower at 24 hours and during the first months of therapy. However, by 5 months, plasma angiotensin II levels had returned to normal. Thus, increased bradykinin may be important in the long-term blood pressure effect of ACEIs. A recent study showed that a bradykinin-receptor antagonist significantly attenuated the ACEI blood pressure effect. Animal studies suggest that ACEI-induced bradykinin may also be important in reducing morbidity and mortality in cardiomyopathy and after an MI.[6,8]

ANGIOTENSIN II-RECEPTOR BLOCKERS

Angiotensin II-receptor blockers (ARBs) are equipotent to ACEIs, β-blockers, diuretic agents, and calcium channel blockers for lowering blood pressure in a general population. Compared with placebo, ARBs have similar rates of adverse effects. Patients have no dry cough (bradykinin breakdown is unaffected; figure 4 and figure 6).[21] Few cases of ARB-induced angioedema have been reported. However, given that many patients have received ARB without incurring angioedema after conversion from an ACEI, this should be a relative contraindication for ARB use.

Renal disease

Pilot studies suggest that the progression of renal disease in patients with type 1 and type 2 diabetes mellitus can be slowed with ARBs to a similar degree as seen with ACEIs.[22,23] Trials are under way in patients with type 2 diabetes who have proteinuria to assess ARB effects on morbidity and mortality.[24-26]

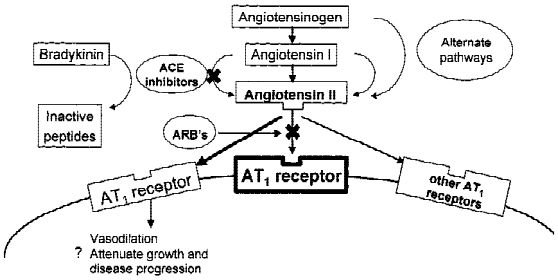


Figure 6 Mechanism of action of angiotensin II-receptor blockers (ARBs) (adapted from Weir and Dzau[21]). AT_1 = angiotensin II-receptor type 1.

After MI

Data from studies in animals suggest that LVEFs after MI may be improved and reperfusion arrhythmias reduced with ARB use compared with ACEIs.[6] Two trials are under way that compare the use of ARBs with that of ACEIs in patients who have had MI and who have reduced LVEFs.[27,28]

CHF

The study Evaluating Losartan in the Elderly (ELITE) was the first to suggest comparable safety and efficacy between ARBs and ACEIs in patients with CHF.[29] Participants with New York Heart Association class II to IV heart failure (n=722; mean age, 72 years) with LVEFs of less than 40% who were not previously treated with ACEIs were randomly allocated to receive losartan potassium or captopril.[29] The primary end point of increased serum creatinine levels occurred in 10.5% of each group. Adverse effects were lower with the use of losartan (44 vs 77 patients; $P<0.002$). The hospitalization rate for CHF was 5.7% in each group. Mortality was lower with losartan use (4.8%) than with captopril (8.7%; $P = 0.04$), an important finding because we know that ACEIs reduce mortality in patients with CHF.

In the larger ELITE-II trial, patients older than 60 years with LVEFs of less than 40% were again randomly assigned to treatment with either losartan or captopril.[30] Losartan and captopril were equally efficacious in the treatment of patients with CHF. The authors concluded that although ARBs have not been proved to be substitutes for ACEIs, they may be a safe and effective alternative in ACEI-intolerant patients who have CHF.

ACEI IN COMBINATION WITH ARB

The use of ACEIs improves morbidity and mortality in patients with CHF, possibly through increased bradykinin levels. Blocking angiotensin II-receptor binding with ARBs may offer comparable benefit. Would combination therapy be better than either drug alone for treating CHF? In 4 pilot studies, patients with CHF on long-term ACEI therapy were randomly allocated to receive ACEI, ARB, or combination therapy.[31-34] Beneficial end points with combination therapy included additional blood pressure lowering and improved exercise tolerance, New York Heart Association classification, and LVEFs.

The Valsartan Heart Failure Trial (VAL-HeFT; presented at the American Heart Association 2000 Scientific Sessions). was the first large trial to determine if there was incremental value in adding an ARB to long-term ACEI therapy in patients with CHF. Patients with New York Heart Association class II to IV CHF who had LVEFs of less than 40% were randomly allocated to receive valsartan or placebo (n=5,010; 93% receiving long-term ACEI therapy). There was a small (13%) reduction in the primary end point of combined mortality, sudden cardiac death, CHF hospitalization, or need for intravenous CHF medical therapy ($P<0.01$). This was primarily due to a 27% reduction in CHF hospitalizations, with no significant effect on mortality. Positive secondary end points included improvement in LVEFs and quality of life.

CONCLUSIONS

ACEIs remain first-line therapy in patients with hypertension and concurrent CHF, proteinuria, or who have had an MI, because their use lowers morbidity and mortality in each of these types of patients. For patients who cannot tolerate ACEIs, ARBs may offer an alternative, especially in patients with CHF, for whom more data with ARBs are available. Future trials will confirm whether adding ARB to the medical regimen of these patients already taking an ACEI will add significant incremental value. Which class of drugs will be first-line therapy in the future? If pending studies show that ARBs are as good, if not better, than ACEI therapy with fewer side effects, ARBs may replace ACEIs in the treatment of these patients.

Franklin Delano Roosevelt suffered many cardiovascular consequences of untreated hypertension. During the last year of his presidency, while guiding the United States through World War II, FDR was plagued with CHF, renal disease, and angina and died of a cerebrovascular event. It is obvious that he would have benefited on many levels from a medication that attacked the renin-angiotensin system.

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capsule

Walking can burn more calories than jogging People may burn more calories by abandoning the pretense of "going for a run" and going for a walk at the same speed instead (*J Sports Med Phys Fitness* 2001;40:297-302). A study of volunteers on treadmills shows that walking a mile at 5 miles per hour uses up at least as much energy as jogging a mile at the same pace. The volunteers were all healthy women who were walking normally, not race walking.

capsule

The hazards of color blindness Because of their inability to distinguish red from green, color-blind men can have trouble recognizing blood in their bodily fluids. In a study reported in *Archives of Internal Medicine* (2001;161:461-465), 10 color-blind volunteers were less likely than the control group to spot blood in photographs of sputum, urine, or stool. In theory, this could delay the diagnosis of a dangerous malignancy. Perhaps questions about color blindness should be part of routine clinical examinations.